nature medicine

Perspective

https://doi.org/10.1038/s41591-023-02513-2

A new clinical classification of acute myocardial infarction

Received: 19 May 2023

Accepted: 26 July 2023

Published online: 27 August 2023

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The existence of a universal definition of myocardial infarction—which involves classification into multiple subtypes—has promoted the use of standard diagnostic criteria across the world. However, this classification has not been applied consistently in practice and is perceived by some as too complicated. Where there is diagnostic uncertainty, patients have worse outcomes. This uncertainty has also impacted on the validity of the diagnosis of myocardial infarction in clinical trials. To address these issues and to encourage clinicians to recognize that different mechanisms of myocardial infarction have differing treatment implications, we propose an alternative clinical classification for consideration; one that recognizes that myocardial infarction can arise spontaneously, secondary to another condition, or as a complication of a cardiac procedure. This classification is aligned with clinical practice and proposes more objective and specific diagnostic criteria that, if agreed by international consensus, could reduce diagnostic uncertainty in practice and research.

The accurate diagnosis of acute myocardial infarction is essential to ensure timely treatment to limit the extent of myocardial injury and prevent complications, such as heart failure or sudden cardiac death. To standardize the diagnostic criteria for myocardial infarction and encourage the application of these standards worldwide, the universal definition of myocardial infarction was proposed and endorsed by the World Health Organization and major national and international cardiac societies[1–3]. This has been an important global effort, but, like all scientific and medical standards, it requires regular review and revision as new evidence emerges.

The current definition states that the term 'acute myocardial infarction' should be used when there is acute myocardial injury with clinical evidence of myocardial ischemia. Several criteria must be met for a diagnosis of myocardial infarction—including a rise and/or fall in circulating cardiac troponin with at least one value above the 99th percentile upper reference limit—and the 2007 iteration introduced five subtypes of myocardial infarction[2] (Box 1). The most recent iteration (in 2018) introduced the term myocardial injury to describe any elevation in cardiac troponin above the 99th percentile[4], irrespective of whether this is due to ischemic or nonischemic mechanisms.

Despite the logic of the latest definition of myocardial infarction, this classification has been perceived by some as too complicated and adoption in clinical practice and in research has been inconsistent. In this Perspective, we first outline the controversies and challenges that have arisen in applying the current classification. We then propose an alternative clinical classification with more objective diagnostic criteria, for consideration by the scientific community. Lastly, we describe the steps required to achieve a new consensus.

Controversies and challenges with the current classification

Some recommendations from the current classification are considered controversial. Type 2 myocardial infarction (Box 1) currently encompasses both coronary mechanisms (such as spontaneous dissection, embolism or vasospasm) and noncoronary mechanisms (resulting from tachycardia, hypotension, hypoxia or anemia), the latter of which can occur in patients with or without underlying coronary artery disease. Different treatments are needed for each of these scenarios, which has limited the utility of this diagnosis in practice. Furthermore, there is often uncertainty in how to distinguish type 1 from type 2 myocardial infarction, and type 2 myocardial infarction from nonischemic

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https://doi.org/10.1038/s41591-023-02513-2

BOX 1

The current standard: universal definition of myocardial infarction

The diagnosis requires a rise and/or fall in cardiac troponin with at least one value above the 99th percentile upper reference limit and any one of the following: symptoms of myocardial ischemia, new ischemic changes on the electrocardiogram, imaging evidence of new loss of viable myocardium or the identification of thrombosis on coronary angiography.

Type 1 myocardial infarction is limited to patients with coronary atherothrombosis and is specified when plaque rupture or erosion results in partial or complete coronary occlusion, myocardial ischemia and necrosis. Type 2 myocardial infarction identifies patients where myocardial ischemia and necrosis occur as a consequence of an imbalance between myocardial oxygen supply or demand unrelated to coronary atherothrombosis. Type 3 myocardial infarction is defined as cardiac death where myocardial infarction is the likely cause, but the death occurred before diagnostic testing could be performed. The classification was further updated in the third and fourth iterations[3,4], introducing additional subgroups following percutaneous coronary intervention (type 4a), stent or scaffold thrombosis (type 4b) or in-stent restenosis (type 4c), and to refine the criteria for myocardial infarction following cardiac surgery (type 5).

myocardial injury in practice[5]. Type 4 and type 5 myocardial infarction are rarely applied to describe periprocedural complications in practice and the diagnostic criteria are debated by cardiologists and cardiac surgeons alike—with disagreement regarding the cutoff values for cardiac troponin elevation and whether additional evidence of a complication is required[6]. The following paragraphs expand on key factors that have limited adoption and generated uncertainty.

First, the classical description of ischemic symptoms was derived from studies dominated by patients with type 1 myocardial infarction. Studies have shown that classical symptoms (chest pain radiating to the jaw, neck, back, arm or shoulder) are less common in patients with type 2 than in those with type 1 myocardial infarction[7]. Dyspnea is a particularly challenging symptom in this context, as it is relatively common and has both ischemic and nonischemic causes. Furthermore, patients with type 2 myocardial infarction usually have other symptoms due to the condition triggering oxygen supply–demand imbalance—making it even more difficult to determine whether symptoms are caused by myocardial ischemia.

Second, while electrocardiographic findings of ST-segment elevation or depression strongly indicate an acute coronary event (such as type 1 or type 2 myocardial infarction due to coronary causes), other less-specific changes on the electrocardiogram (or no changes at all) are also common in both myocardial infarction and acute myocardial injury[8].

Third, elevation in circulating cardiac troponin is a prerequisite for the diagnosis of myocardial infarction. However, recent research has challenged not only the concept that elevation of cardiac troponin always represents cardiomyocyte death[9], but also that cardiac troponin elevation in the context of myocardial ischemia always represents necrosis[10]. The introduction of high-sensitivity cardiac troponin assays has enabled earlier diagnosis[11], but has decreased the specificity of cardiac troponin for myocardial infarction[8]. Furthermore, elevation in cardiac troponin is an inevitable consequence of cardiac surgery[12,13] and is common and often asymptomatic following coronary intervention[14]. As such, the diagnostic threshold for myocardial infarction following coronary intervention and cardiac surgery is arbitrarily set at greater than five and ten times the 99th percentile upper reference limit, respectively[4].

Fourth, it is not possible to distinguish type 1 from type 2 myocardial infarction due to dissection, spasm or embolism, without performing coronary angiography. If angiography is not performed, patients with coronary causes of type 2 myocardial infarction will almost certainly be classified incorrectly as type 1. Similarly, since coronary angiography is seldom performed in patients thought to have type 2 myocardial infarction[8,15–17], an unknown proportion will actually have had a type 1 myocardial infarction.

Finally, in the current classification, evidence of imbalance between myocardial oxygen supply or demand is a prerequisite for a diagnosis of type 2 myocardial infarction, which means that an underlying trigger must be identified. Sometimes the trigger is obvious, but often the mechanism is unclear. The ischemic threshold will vary in relation to the duration and magnitude of supply–demand imbalance, and the extent and severity of underlying coronary artery disease[18]. The current classification even allows for the diagnosis of type 2 myocardial infarction to be made in patients without coronary artery disease, despite this being the hallmark of acute myocardial infarction for more than a century[19] and one of the main determinants of long-term prognosis[20].

These uncertainties arise every day in clinical practice and have important consequences for patient care. Where there is diagnostic uncertainty, patients have worse outcomes[21]. Many patients fulfilling the criteria for type 2 myocardial infarction are not classified as such in practice as the diagnosis is not considered important by some clinicians[22]. While there is a wealth of evidence to guide how patients with type 1 myocardial infarction should be managed, there is no evidence or agreement on how patients with type 2 myocardial infarction or acute myocardial injury should be managed, and no studies demonstrating that recognition of these conditions improves outcomes[23]. The current classification is perceived by some as too complicated and has resulted in a lack of agreement even among experts. As such, the classification has been used and interpreted in different ways in the development of early diagnostic pathways[24–27] and in clinical trials of coronary revascularization[28], making it difficult to compare findings between studies.

A new clinical classification of myocardial infarction

To address these uncertainties and encourage clinicians to recognize that there are different mechanisms of myocardial infarction with differing treatment implications, we propose a simplified clinical classification that recognizes myocardial infarction can arise in three clinical settings: spontaneously, secondary to another acute condition or as a procedural complication following percutaneous intervention or cardiac surgery (Fig. 1). To increase adoption in practice, we propose diagnostic criteria that are more specific, less reliant on symptoms and electrocardiographic changes and more aligned with clinical practice (Table 1).

For the diagnosis of spontaneous myocardial infarction, the definition needs to be as sensitive as possible, as failure to recognize an acute coronary syndrome may delay the initiation of treatment—potentially resulting in a more substantial myocardial infarction with ventricular impairment or cardiac death in the community. By contrast, for secondary or procedural myocardial infarction, the diagnostic criteria should be more specific to minimize uncertainty, as cardiac troponin elevation is common in these settings. Here, the diagnosis of myocardial infarction should identify patients in whom there are clear treatment implications. The classification of type 3 myocardial

https://doi.org/10.1038/s41591-023-02513-2

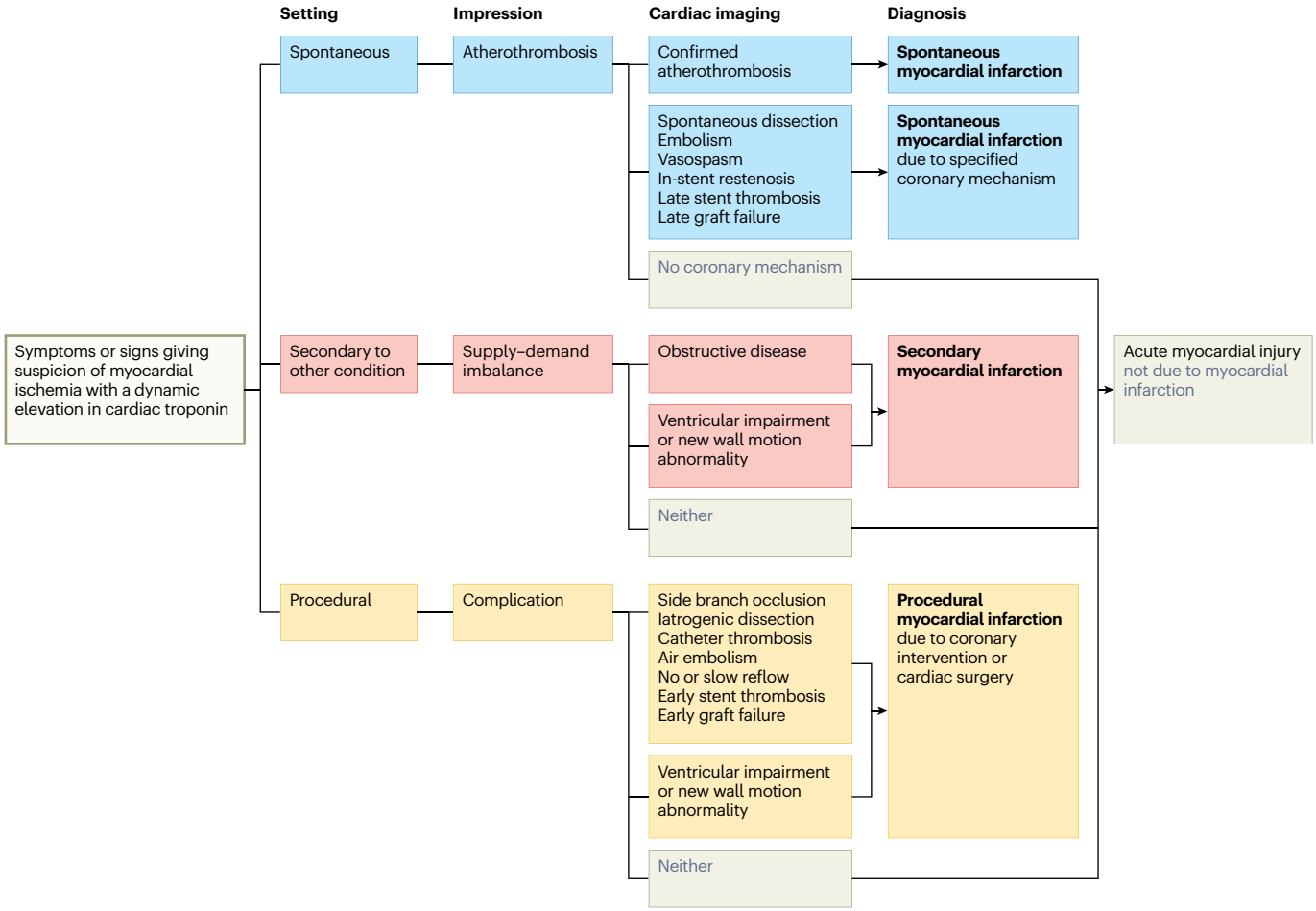

Fig. 1 | Proposal for a clinical classification of acute myocardial infarction. Spontaneous myocardial infarction: while the initial impression is often confirmed following coronary angiography or echocardiography, other conditions can present similarly. If no coronary mechanism is evident, echocardiography or cardiac magnetic resonance imaging may be required to identify alternative causes of acute myocardial injury, such as takotsubo cardiomyopathy or myocarditis. Secondary myocardial infarction: the diagnosis of secondary myocardial infarction due to an alternative condition requires evidence of a new regional wall motion abnormality or left ventricular impairment on echocardiography, or evidence of loss of viable myocardium on magnetic resonance imaging, or the presence of obstructive coronary artery disease on invasive or computed tomography coronary angiography. Patients with acute myocardial injury in this setting for whom secondary myocardial infarction is thought unlikely or has been excluded, may benefit from cardiac imaging to identify other nonischemic structural heart diseases unmasked by acute illness. Procedural myocardial infarction: Coronary complications following percutaneous coronary intervention are usually self-evident, but following cardiac surgery routine echocardiography to recognize asymptomatic procedural myocardial infarction should be performed in the postoperative period.

infarction (per the current definition) would become obsolete. If a patient died suddenly from what was thought to be myocardial infarction before undergoing testing, this would be classified as spontaneous, secondary or procedural myocardial infarction depending on the setting.

Spontaneous myocardial infarction

In patients with the spontaneous onset of symptoms or signs suspicious of myocardial ischemia, treatment is initiated on the assumption that atherothrombosis is the underlying mechanism—and in most cases, this assumption is correct. However, there are other causes of spontaneous presentation with myocardial infarction, including coronary dissection, embolism and vasospasm; or late stent thrombosis, restenosis and late graft failure in those with prior revascularization[29]. In practice, clinicians should be encouraged to identify the underlying coronary mechanism through angiography with or without adjunctive intravascular imaging, and to tailor subsequent treatment accordingly.

The terms ST-segment elevation and non-ST-segment elevation for spontaneous myocardial infarction will remain useful to stratify patients at presentation, and to indicate the timing of coronary angiography. However, they are less useful to guide subsequent management than a classification identifying the underlying coronary mechanism, as proposed here. In some settings where the patient does not have ongoing symptoms or ST-segment elevation, it may be reasonable to treat for atherothrombosis without performing coronary angiography—particularly if the risks of an invasive procedure are prohibitive or in healthcare settings where access is limited, and especially if there is a high clinical likelihood this is the underlying mechanism. In younger patients without traditional cardiovascular risk factors or in those with prior revascularization, alternative coronary mechanisms of spontaneous myocardial infarction may be more likely and coronary angiography should be encouraged.

Irrespective of the coronary mechanism, the definition of spontaneous myocardial infarction should prioritize sensitivity; therefore, clear symptoms or signs of myocardial ischemia with a rise and/or fall in cardiac troponin above the 99th percentile upper reference limit may be sufficient to make the diagnosis, and further imaging evidence of infarction may not be required. However, if no coronary mechanism is evident following coronary angiography, echocardiography or cardiac magnetic resonance imaging should be considered to clarify the

https://doi.org/10.1038/s41591-023-02513-2

Table 1 | Diagnostic criteria for the universal definition and the proposed clinical classification of myocardial infarction

Universal definition	Proposed clinical definition	Rationale for change
Type 1 myocardial infarction	**Spontaneous myocardial infarction**	
Sensitivity prioritized, with the diagnosis based on a rise and/or fall in cardiac troponin above the 99th percentile with symptoms or signs of myocardial ischemia.	Sensitivity prioritized, with the diagnosis based on a rise and/or fall in cardiac troponin above the 99th percentile with symptoms or signs of myocardial ischemia.	Sensitivity is important to minimize the risk of misdiagnosis of all acute coronary mechanisms of myocardial infarction, not just those due to atherothrombosis.
Restricted to coronary atherothrombosis	Criteria broadened to include all acute coronary events: atherothrombosis, embolism, vasospasm, in-stent restenosis, late stent thrombosis and late graft failure.	Late stent and graft failure are often spontaneous due to de novo disease rather than procedural complications.
Type 2 myocardial infarction	**Secondary myocardial infarction**	
Sensitivity prioritized, with the diagnosis based on a rise and/or fall in cardiac troponin above the 99th percentile with symptoms or signs of myocardial ischemia.	Specificity prioritized, with the diagnosis based on loss of viable myocardium or new regional wall motion abnormality, or the presence of obstructive coronary artery disease.	Symptoms and signs of myocardial ischemia are challenging to differentiate from those due to a primary condition. Myocardial injury is common and may be caused by many different mechanisms.
Documentation of myocardial oxygen supply or demand imbalance is required, which includes spontaneous coronary dissection, embolism and vasospasm, and those with other conditions without coronary artery disease.	Can occur in any acute illness where myocardial oxygen supply or demand imbalance could arise, but must have a functional consequence or unmask obstructive coronary artery disease.	Diagnostic criteria should be more specific to minimize uncertainty and identify patients in whom the diagnosis has clear treatment implications.
Type 3 myocardial infarction		
Cardiac death where myocardial infarction is the likely cause, but death occurs before diagnostic testing is performed.	No longer required.	No utility in clinical practice and death from myocardial infarction can occur due to multiple mechanisms before testing.
Type 4a–c myocardial infarction	**Procedural myocardial infarction**	
Type 4a is based on an arbitrary elevation in cardiac troponin greater than five times the 99th percentile if there are signs of myocardial ischemia, imaging evidence of new loss of viable myocardium or angiographic evidence of a procedural complication within 48 h.	Specificity prioritized, with diagnosis requiring angiographic evidence of a complication of coronary intervention or cardiac surgery and new left ventricular impairment, loss of viable myocardium or a regional wall motion abnormality.	Cardiac troponin thresholds are not evidence based and testing is not performed in clinical practice following coronary intervention or cardiac surgery.
Type 4b due to stent thrombosis and type 4c due to restenosis can occur any time after the procedure. The same diagnostic criteria are applied as those for type 1 myocardial infarction.	Definition broadened to include any stent or graft failure within 30 days of the procedure.	Captures all clinically important failures of coronary revascularization within 30 days. Late stent and graft failure are not considered complications of revascularization.
Type 5 myocardial infarction		
Diagnosis based on an arbitrary elevation in cardiac troponin concentration greater than ten times the 99th percentile if there are new pathological Q-waves, imaging evidence of new loss of viable myocardium or angiographic evidence of a graft occlusion within 48 h.	See above for 'Procedural myocardial infarction'.	Addresses inconsistencies between the criteria for diagnosing myocardial infarction following coronary intervention and cardiac surgery, allowing a fairer comparison of outcomes between approaches.

diagnosis or identify alternative causes of the presentation and acute myocardial injury, such as takotsubo cardiomyopathy or myocarditis.

Secondary myocardial infarction

In patients with symptoms or signs that are suspicious of myocardial ischemia secondary to another acute illness that results in myocardial oxygen supply–demand imbalance, the initial priority is to manage the acute illness. Cardiac troponin testing in acute illness identifies a substantial proportion of patients with myocardial injury of uncertain cause or clinical relevance[30]. In this setting, specificity rather than sensitivity is important, and the diagnosis of secondary myocardial infarction is likely to be better accepted by clinicians and patients if injury is associated with functional consequences. The diagnosis of secondary myocardial infarction should require the identification of new loss of viable myocardium or a regional wall motion abnormality, on echocardiography or cardiac magnetic resonance imaging. This is one of several possible criteria for a diagnosis of myocardial infarction in the existing universal definition[4], but it should be essential for the diagnosis of secondary myocardial infarction. The only exception would be where myocardial ischemia or myocardial injury in the context of another acute illness unmasks the presence of obstructive coronary artery disease on invasive or computed tomography coronary angiography[18,31]. In both circumstances, the diagnosis of secondary myocardial infarction would have treatment implications because secondary prevention, medical therapy or coronary revascularization may prevent recurrent symptoms and future cardiovascular events. However, most patients with supply–demand imbalance will have neither new loss of viable myocardium nor obstructive coronary artery disease. Here, the term acute myocardial injury is a good description—similar to acute kidney or liver injury—with prognostic implications that should stimulate further investigation but not be considered a definitive diagnosis.

Procedural myocardial infarction

The use of more sensitive diagnostic criteria for procedural myocardial infarction, proposed in the universal definition, has not been embraced by practitioners or applied in clinical trials of coronary revascularization[6]. In defining a procedural complication, specificity is more important than sensitivity. The diagnosis of myocardial infarction is appropriate in patients with an overt complication of coronary intervention or cardiac surgery, or in those where the complication is less obvious but new left ventricular impairment or loss of viable myocardium with a regional wall motion abnormality is identified. Coronary complications following percutaneous coronary intervention

are usually self-evident, but following cardiac surgery, echocardiography to identify unrecognized procedural myocardial infarction should be systematically performed in the postoperative period. Procedural myocardial infarction defined in this way is important as it gives direct insight into the effectiveness of revascularization, and may have treatment implications. Acute or subacute stent thrombosis and early graft failure within 30 days are recognized complications of revascularization and should be classified as procedural myocardial infarction[32]. By contrast, late stent or graft failure is often a consequence of de novo disease or noncompliance with antiplatelet therapy and therefore should be classified as spontaneous myocardial infarction rather than a procedural complication. Myocardial injury following a cardiac procedure has been associated with poor prognosis in some studies[12] and could be used to support the evaluation of quality of care, but on its own it should not be considered a complication unless a coronary mechanism or new regional wall motion abnormality or ventricular impairment is identified on cardiac imaging.

Knowledge gaps and potential limitations

We acknowledge that further research is needed to evaluate the potential impact of this proposed new definition of myocardial infarction on patient care and healthcare utilization. This could take advantage of existing clinical datasets from well-characterized patient populations to retrospectively compare the current classification with the proposed clinical classification. However, prospective studies will also be needed, in which cardiac imaging is performed systematically. Also, there are potential limitations of the proposed classification that merit consideration.

First, although the proposal aims to simplify the classification of myocardial infarction and remove the need for an alphanumeric subclassification that clinicians will not remember or apply, we recognize the importance of identifying the different coronary mechanisms of spontaneous myocardial infarction. Most patients with spontaneous myocardial infarction will have atherothrombosis and will receive a diagnosis of 'myocardial infarction due to atherothrombosis' or simply 'myocardial infarction' in practice. However, where spontaneous myocardial infarction is a consequence of an alternative coronary mechanism, the final diagnosis would identify this; for example, 'myocardial infarction due to coronary embolism' or 'myocardial infarction due to late stent thrombosis'.

Second, we recognize that for a diagnosis of secondary myocardial infarction, it may be challenging to determine whether a regional wall motion abnormality on imaging is old or new. Where a patient is known to have coronary artery disease or previous myocardial infarction, then comparison with previous imaging may be helpful. Where there is no prior history, then the identification of any regional wall motion abnormality is important and would have therapeutic implications. While often it is possible to differentiate an acute from chronic infarct pattern on echocardiography or magnetic resonance imaging (based on thinning of the myocardium or the presence of edema), some clinical judgment will be required.

Finally, by defining more specific and objective criteria for the diagnosis of secondary myocardial infarction, we do not wish to undermine the importance of recognizing those with acute myocardial injury. We hope that our proposal will encourage the use of cardiac imaging in this setting and improve the care and outcomes of patients with and without secondary myocardial infarction. While imaging may rule out secondary myocardial infarction, it could identify other important clinical diagnoses, such as heart failure or pulmonary embolism, or it could identify patients with unobstructive coronary artery disease in whom the use of secondary prevention may be beneficial.

Future directions

Our proposal is based on new research and our clinical observations; however, we acknowledge that any change in practice will require a new international consensus as changes to the current universal definition would have important implications for clinicians, coders, researchers and clinical trialists. A new global task force will need to be convened with input from a broad range of stakeholders—including both patients and practicing clinicians across a range of specialties, in addition to people with expertise in cardiac biomarkers, coronary intervention, cardiac surgery, clinical trials and international registries. Greater diversity and wider representation are needed if we are to achieve consensus on the need for a more applied classification.

Once international consensus has been reached, it would be important to propose additional supplementary codes beyond the primary classification within the eleventh revision of the International Classification of Diseases (ICD-11). These supplementary codes would enable standard hospital coding for the different mechanisms of spontaneous myocardial infarction (for example, diagnostic code BA82 for coronary artery dissection, BA85 for coronary vasospasm and others), secondary myocardial infarction and procedural myocardial infarction following percutaneous intervention and cardiac surgery. These should be published in parallel to the consensus statement and combined with educational initiatives, as well as a systematic evaluation of the impact of implementation of a new classification of myocardial infarction on patients and healthcare systems.

Conclusion

The classification of myocardial infarction is important for patients, practice and research. We propose a new approach that prioritizes sensitivity for patients with spontaneous coronary events, and specificity for those with oxygen supply–demand imbalance secondary to other conditions, or complications from coronary intervention or cardiac surgery. We argue that such an approach may encourage adoption in practice and improve patient care, and we encourage research and debate with the goal of a new international consensus.

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Acknowledgements

B.L. was a member of the Task Force for the Universal Definition of Myocardial Infarction. N.L.M. is supported by a Chair Award (CH/F/21/90010), Programme Grant (RG/20/10/34966) and a Research Excellent Award (RE/18/5/34216) from the British Heart Foundation.

Author contributions

B.L. and N.L.M. drafted and revised the manuscript critically for important intellectual content, provided approval of the final version to be published and are accountable for the work.

Competing interests

B.L. declares no competing interests. N.L.M. reports research grants awarded to the University of Edinburgh from Abbott Diagnostics and Siemens Healthineers, and honoraria from Abbott Diagnostics, Siemens Healthineers, Roche Diagnostics and LumiraDx.

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Peer review information *Nature Medicine* thanks Adnan Kastrati and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Karen O'Leary, in collaboration with the *Nature Medicine* team.

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